Editorials

Regression of Atherosclerosis—An Ounce of Prevention

ELSEWHERE IN THIS ISSUE, Blankenhorn and Hodis summarize the findings of a quarter century of clinical investigation into the possibility that atherosclerotic arterial obstruction may be reversed or regressed.[1] To date, the arteriogram has been the principal tool used to address this question in patients. But as Blankenhorn and Hodis point out, the underlying pathologic processes are complex. Furthermore, the arteriogram is not useful for resolving the biologic and structural processes resulting in clinical disease or for deciphering those mechanisms accounting for the beneficial effects of therapy. To begin to understand the clinical relevance of atherosclerosis regression, we must integrate information and ideas from many sources and disciplines besides angiography—from autopsies, from cell biology and experimental pathology, and from epidemiology, pharmacology, and metabolism, among others.

Current knowledge about atherosclerosis regression comes largely from experiments in animals and from clinical arteriographic studies. The basic term regression implies one thing to experimental pathologists and another to clinicians. To pathologists, regression means the shrinkage of intimal plaque through a reduction in its major components: smooth muscle, macrophages, connective tissues, and lipid. To physicians interpreting human disease by its arteriographic appearance, regression is defined as an enlargement in the caliber of the narrowed arterial lumen. Such improvement seldom occurs in the natural course of the disease. Because these arteriographic images do not permit an easy distinction among the various mechanisms of regression, our understanding of the principal process(es) by which it occurs in patients is limited. Regression, so defined, may occur not only by the process of plaque shrinkage but also by a variety of other possible mechanisms. For example, lysis of fully occlusive thrombi or of mural thrombi is commonly seen in the course of unstable ischemic syndromes.[2] Healing may favorably remodel an acutely disrupted plaque.[3] Adaptive enlargement of the underlying arterial architecture can improve arteriographic lumen caliber independently of changes in plaque size.[4] Relaxation of arterial vasomotor tone can similarly enlarge the lumen caliber.[5] The role of the endothelium and the relationship(s) of therapy to its function have been shown to be important in many of these processes.

Thus, the important question is not "does arteriographic regression occur in patients?" (it does), but "can such regression be promoted with a sufficiently great magnitude and frequency to justify a major therapeutic strategy?" Important related questions are "By what mechanism(s) is regression achieved?" and "Does such induced regression provide clinical benefits?" and "If so, by what means?" Although there is no consensus on the answers to these questions, encouraging evidence is emerging.

In the nonhuman primate studies of Armstrong, Small, and colleagues, atherosclerosis has been shown convincingly to regress with lipid-lowering drugs.[6,7] In the typical regression experiment, atherosclerosis is induced by feeding cholesterol to a group of animals. The amount and composition of intimal thickening is subsequently assessed at specified times, using group-averaged chemical and histologic end points. When the animals are returned to their native vegetarian "regression" diet, plasma cholesterol levels fall quickly to normal (140 mg per dl), and the arterial lipid and connective tissue accumulations partially regress over 20 to 40 months.

Not all forms of cholesterol are readily depleted from these cholesterol-rich intimal lesions. The more mobile forms, including cholesteryl esters in foam cells, lipoproteins, and cholesteryl ester droplets, have been shown to diminish in response to reduced plasma cholesterol, but the cholesterol monohydrate crystals of the core lipid region resist mobilization.[7] Histologic measurements show that plaque mass is reduced during regression therapy.[6,7]

Evidence in Humans

Blankenhorn and Hodis provide a complete list of clinical arteriographic studies the results of which suggest that the obstructive process can be retarded or reversed by therapies that result in reduced levels of low-density lipoprotein (LDL)-cholesterol and increased levels of high-density lipoprotein (HDL)-cholesterol. The composite of evidence from these randomized clinical arteriographic trials consistently indicates that existing coronary lesions in untreated patients progressively worsen in severity on average by about 1% stenosis per year.[8] Regression (improvement) is uncommon in the natural course of the disease. Clinical events occur at a rate of about 5% to 10% annually among untreated patients with clinically established coronary disease. By contrast, treating patients intensively with potent lipid-lowering drug and diet combinations has, in many studies, lessened the mean severity of obstruction by about 0.5% stenosis per year. In other studies, lesion progression has been substantially retarded relative to lesions in control patients. These studies generally conclude that such benefit is predicted by favorable alterations in the LDL-:HDL-cholesterol ratio. Even with intensive drug therapy that results in strikingly favorable alterations of the atherogenic lipid profile, regression by an appreciable amount (10% stenosis) occurs infrequently (1 in 3 patients and 1 in 8 diseased arterial segments[8]).

Surprisingly, this modest and infrequently observed regression of arterial obstruction during lipid-lowering therapy is associated with a much more striking reduction in the frequency of clinical cardiovascular events (ischemic death, infarction, or unstable ischemia refractory to medical therapy and requiring revascularizing procedures). For example, in the Familial Atherosclerosis Treatment Study, the incidence of clinical cardiovascular

events (defined as cardiac death, infarction, or revascularization for progressive ischemia refractory to medical therapy) was reduced by 73% with intensive lipid-lowering therapy when compared with a conventional strategy.[9] Of 52 patients randomly assigned to diet and possible colestipol therapy, 10 had such an event, as did 5 of 74 to therapy with either niacin plus colestipol or lovastatin plus colestipol. In the Program on the Surgical Control of the Hyperlipidemias, 838 patients were randomly allocated to partial ileal bypass operation or to usual clinical care.[10] After five years, the ileal bypass group, on average, had a 42% reduction in LDL-cholesterol levels and little change in HDL-cholesterol levels; the usual-care group had an 8% reduction in LDL-cholesterol levels. After ten years, the surgical group had 32 cardiac deaths, 50 nonfatal myocardial infarctions, 52 coronary artery bypass operations, and 15 coronary angioplasties. Corresponding figures in the medically treated group were 44 ($P = .13$), 81 ($P < .001$), 137 ($P < .0001$), and 33 ($P = .005$), respectively. All-cause mortality was reduced 36% ($P = .02$) among the majority with baseline ejection fractions of 0.50 or more. In the St Thomas' Atherosclerosis Regression Study, there were 10 cardiovascular events among 28 patients completing the "usual care" assignment, 3 among 27 completing diet alone ($P < .05$), and 1 among 26 completing diet plus cholestyramine ($P < .01$).[11]

Thus the evidence from angiographic trials demonstrates both coronary artery and clinical benefits from lipid-lowering therapy using any of a variety of treatment regimens. The findings of decreased arterial disease progression and increased regression have been convincing but, at best, modest in their magnitude. In view of these modest arterial benefits, the associated reductions in cardiovascular events have been surprisingly great. On closer examination of the data of the Familial Atherosclerosis Treatment Study, we find that the 73% reduction in the incidence of clinical events in this study is entirely explained by a 93% reduction in the likelihood that a mildly or moderately narrowed arterial segment would substantially progress to become the severe lesion that caused the clinical event.[8] The magnitude of the clinical benefit is best explained in terms of this observation, using the following lines of reasoning[8]:

- Clinical events most commonly spring from lesions that are initially of mild or moderate severity and that abruptly undergo a disruptive transformation to a severe "culprit" lesion.[12]
- The process of plaque fissuring leading to plaque disruption and thrombosis triggers most clinical coronary events.[13] Fissuring is predicted by a large accumulation of core lipid in the plaque and by a high density of lipid-laden macrophages in its thinned fibrous cap.[14] Lesions with these characteristics make up only 10% to 20% of the overall lesion population but account for 80% to 90% of the acute clinical events.
- In the experimental setting, normalization of an atherogenic lipid profile substantially decreases the number of lipid-laden intimal macrophages (foam cells) and gradually depletes cholesterol from the core lipid pool.[6,7] As above, these two aspects of plaque composition are predictors of subsequent plaque instability. Thus a normal lipid profile should result in plaque stability.
- In the clinical setting, intensive lipid-lowering therapy virtually halts the progression of mild and moderate lesions to severe obstructions, thus preventing clinical events.[8,9]

In conclusion, the reduction in clinical events observed in these human arteriographic trials appears to be best explained by the relationship of the lipid and foam cell content of the atherosclerotic plaque to its likelihood of fissuring and by the effects of lipid-lowering therapy on these "high risk" plaque features. The composite of data presented here supports the hypothesis that lipid-lowering therapy selectively depletes lipid (regresses) in that relatively small but dangerous subgroup of "vulnerable" fatty lesions containing a large lipid core and dense clusters of intimal macrophages. By doing so, these lesions are effectively stabilized, and the clinical event rate is accordingly decreased. Thus, in the course of such treatments, this small lessening in overall disease severity and the relatively infrequent occurrence of definite lesion regression represents the "ounce of prevention" that, by stabilizing the vulnerable plaques, far outweighs the "pound of cure" (revascularization, restriction of lifestyle) associated with unnecessary clinical ischemic events.

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Ectopic Pregnancy—Becoming a Nonsurgical Disorder

THE INCIDENCE OF ectopic pregnancy has been gradually rising, accounting for almost 2% of all pregnancies. Ectopic pregnancy has become a leading cause of maternal morbidity and mortality.[1]

Accurate and early diagnosis is essential for the appropriate use of conservative medical and surgical treatment of ectopic pregnancy.[2,3] In appropriate cases, expectant management may be an option. Ectopic pregnancy can become a "nonsurgical disorder" with early nonsurgical diagnosis and medical management with methotrexate in physicians' offices.[4] The effectiveness of methotrexate therapy is enhanced when given early (ectopic mass < 3.5 cm, no fetal cardiac activity, and human chorionic gonadotropin [hCG] level < 15,000 IU per liter [15,000 mIU per ml]).[5] Most women with ectopic pregnancy who are not candidates for methotrexate therapy can be treated surgically through the laparoscope on an outpatient basis.[6] Laparotomy and hospital admission will be necessary in a few patients who are hemodynamically unstable. In addition to minimizing surgical intervention, early diagnosis and treatment may improve fertility following ectopic pregnancy. The cost savings of early diagnosis and treatment could be enormous. Outpatient methotrexate treatment could cost as little as $500 compared with $5,000 to $15,000 for surgical treatment.

Patients with ectopic pregnancies still present with tubal rupture and compromised hemodynamic status and consequently require emergency laparotomy. Both patients and medical staff must be better educated. No diagnostic test is useful until it is ordered. For women who have risk factors for ectopic pregnancy, there must be a high degree of suspicion in the presence of abnormal vaginal bleeding and abdominal pain. A sensitive hCG assay must be done as soon as pregnancy is suspected. Primary care and emergency department physicians must also have a high degree of suspicion and diligently observe high-risk patients during early pregnancy.

A single quantitation of hCG cannot be used to separate ectopic versus normal pregnancies unless correlated with an ultrasonogram of the pelvis. The major value of hCG levels is in establishing discriminatory zones when ultrasonography can be used to rule out intrauterine pregnancy. Physicians must establish their own discriminatory zone. Factors affecting minimum values of hCG needed to visualize an intrauterine pregnancy include the reference standard for hCG levels, abdominal versus vaginal ultrasonography,[7] and ultrasonographic experience. Serial quantitative hCG titers have become the standard for assessing viability in early pregnancy, with a rate of rise of less than 66% over 48 hours in most nonviable pregnancies. Because as many as 20% of ectopic pregnancies can have normally rising hCG titers, serial hCG titers are often used to determine when a discriminatory level of hCG is reached to appropriately time an ultrasound examination. Extra care is needed to interpret hCG values in patients at high risk for multiple pregnancy (ovulation induction and in vitro fertilization). The demise of one twin may result in temporary plateauing or falling of hCG levels with the remaining twin surviving.

Ultrasonography is used most often to exclude ectopic pregnancy by diagnosing an intrauterine gestational sac; the likelihood of both an intrauterine and ectopic pregnancy is only 1 in 30,000. As ultrasound technology and skill improve, an increasing number of ectopic pregnancies (as many as 70%) can be visualized by ultrasonography. Vaginal sonography has lowered the discriminatory zone for hCG (1,000 to 2,000 IU per liter for vaginal and 6,000 to 6,500 IU per liter for abdominal), thus lowering the gestational age at diagnosis. Vaginal sonography is also used to assess additional adnexal disorders (ovarian cysts and hydrosalpinx), the presence of fluid in the peritoneal cavity, the presence of fetal cardiac activity, and the size of the ectopic pregnancy. All of these sonographic findings will influence the selection of appropriate treatment.

Because serial hCG assessment results in a 48-hour delay in the diagnosis, the single assessment of serum progesterone concentrations has been used to assess fetal viability. A high predictive value is associated with progesterone values of more than 80 nmol per liter (25 ng per ml) for viable and less than 16 nmol per liter (5 ng per ml) for nonviable fetuses.[8] Patients with progesterone concentrations of less than 80 nmol per liter may benefit from ultrasonic evaluation to increase the likelihood of the early diagnosis of ectopic pregnancy. Because of considerable assay variation, each laboratory will have to establish its own threshold values. The progesterone level is of little value in differentiating early miscarriage from ectopic pregnancy.

There may be no role for culdocentesis in the contemporary diagnosis and management of ectopic pregnancy.[9] Culdocentesis is a painful, invasive, nonspecific test that adds little if the above test results are available quickly and accurately. A hemodynamically unstable patient with fluid found in the peritoneal cavity by ultrasonography needs prompt surgical treatment whether or not blood is found on culdocentesis. The presence of blood on culdocentesis in a hemodynamically stable patient does not obviate expectant management (transiently bleeding corpus luteum cyst) or medical or laparoscopic management in appropriate patients.

The cornerstones of the early diagnosis of ectopic pregnancy remain a high index of suspicion, sensitive quantitative hCG assay, and transvaginal pelvic ultrasonography. The widespread use of existing diagnostic